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Name

March 31, 2003
Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: J. Clark & C. Denning

Filing Date: June 13, 2000

Serial No: 09/593,316

Docket: 730/002

Title: ANIMAL TISSUE FOR XENOTRANSPLANTATION

Art Unit: 1632

Examiner: Quan J. Li, Ph.D.

RESPONSE TO OFFICE ACTION
UNDER 37 CFR § 1.116

Commissioner for Patents and Trademarks
Washington, D.C. 20231

Dear Sir,

This paper is responsive to the final Office Action on the merits, dated January 30, 2003 (Paper No. 17), for which a response is due April 30, 2003. The remarks are believed to place the application in condition for allowance, or in better condition for appeal. Accordingly, applicant requests that his paper be entered into the file pursuant to 37 CFR § 1.116.

No amendments are made to the claims or the disclosure in this Response.

This response is being filed within the first two months of the mailing date of the Action. In the event that the application is not allowed, applicant requests an Advisory Action, in accordance with MPEP § 706.07(f).

Status of the application:

This is the third Office Action on the merits of the application. The Office Action indicates that Claims 1-7, 13-17, 22, and 27-37 are pending, and that Claims 1-6 and 33-37 are under examination. In fact, Group II was rejoined into the group under examination, as indicated in the Office Action mailed November 23, 2001 (Paper No. 7). *Thus, the claims under examination are Claims 1-6, 13-15, and 33-37.* In any event, claims 13-15 are rejoinable upon determination that claim 4 is patentable.

Concurrently filed herewith is a Request to Vacate Finality of Office Action as premature, pursuant to 37 CFR §§ 1.104(b) and 1.113(b), and MPEP § 706.07(d). Withdrawal of finality of the Office Action of January 30, 2003 is respectfully requested.

Applicant requests reconsideration and allowance of the application (including all the claims in Groups I, II, and IV).

Interview

Applicant's representative is grateful for the interview conducted with Examiners Janice Li and Deborah Reynolds, at the Patent Office on March 25, 2003. The Examiners question whether α(1,3)galactosyltransferase (α1,3GT) knockout sheep can be made, in view of the information provided by Denning et al. (Nature Biotechnol. 19:559, 2002). In fact, the making of α1,3GT knockout sheep is fully described and enabled in the specification as filed, for reasons explained below.

Viability and phenotype of α1,3GT knockout animals

Accompanying this Response is an Information Disclosure Statement under 37 CFR § 1.97(d), providing a publication which has appeared within the last 3 months. The article is entitled *Production of 1,3-Galactosyltransferase-Deficient Pigs* (Phelps et al., Science 299, 411-414, 2003).

The article describes pigs that are homozygously inactivated for the α1,3GT gene. It confirms that the specification of the present application is enabled for the making of α1,3GT knockout sheep. Observations made in the article include the following:

- Large mammal heterozygous α1,3GT knockout animals can be made, and serve as a suitable source of donor cells for making homozygous knockouts (page 412, col. 1). This is described in the present application *inter alia* on page 38, line 5 to page 40, line 19; and page 41, line 22 to page 42, line 5.
- Homozygous knockout cells can be made by a targeting the other allele in the donor cells using a knockout vector, and selecting cells deficient in the Galα(1,3)Gal surface antigen (page 412, col. 1). This is described in the present application *inter alia* on page 41, lines 9-13 and 17-20; and page 42, lines 6-16.
- Knockout cells can be used as donor cells for nuclear transfer to produce homozygous knockout animals. Four double-targeted female piglets were produced (abstract), of which three had α1,3GT inactivated on both alleles (page 412, col. 3 ff). This is described in the present application *inter alia* on page 38, line 9 to page 40, line 19.
- Homozygous knockout animals are devoid of antibody-detectable Galα(1,3)Gal. See Fig. 1., clones B1-1, B1-2, and B1-4 (the three correctly targeted clones), and Fig. 2. This is described in the present application *inter alia* on page 42, lines 6-24.

Thus, if one has the α1,3GT gene for the species being altered, then large-animal homozygous α1,3GT knockouts can be produced according to the procedures described in the specification, producing cells and tissues devoid of Galα(1,3)Gal. The specification provides the sheep α1,3GT gene — both in the sequence listing, and by way of the biological deposit. This places sheep cells, tissues, and whole animals having a α1,3GT knockout in the hands of the public, in parallel with the illustration provided for the pig α1,3GT gene in the Phelps article.

The Denning reference

The Examiners are concerned that the article entitled *Deletion of the α(1,3)galactosyl transferase (GGTA1) gene and the prion protein (PrP) gene in the sheep* (Nature Biotechnol. 19:559, 2001) provides no actual example of a α1,3GT knockout sheep. However, the article does not support the contention that gene targeting in sheep is an uncertain process. On the contrary — the article provides several illustrations of the viability of the claimed invention:

- Sheep cells can be correctly targeted for inactivation of the α1,3GT gene. See Figure 2, panel (A); and Table 1. This provides a direct illustration of the making of the knockout cells covered by claims 4, 5, and 33-37.
- Targeted cells can be used for nuclear transfer. There are three examples: a) the α1,3GT knockout cell gave rise to viable embryos; b) the PRP knockout cells gave rise to 3 live births; c) viable animals have been produced that were successfully targeted at the COL1A1 locus (ref. 5, discussed on page 559, col. 1).
- *Knocking out the α1,3GT gene does not decrease viability of the embryo.* See the data in Table 2. Nuclear transfer with untransfected donor cells (7G65F4) gave rise to 5 viable fetuses at day 60 in 33 attempts (a 13% success rate). Nuclear transfer of cells treated with the α1,3GT vector but not inactivated (4H2) gave rise to 2 viable fetuses in 23 attempts (an 8% success rate). Nuclear transfer of cells containing an inactivated α1,3GT gene (3C6 and 5E1) gave rise to 5 viable fetuses in 21 attempts (a 19% success rate). Thus, *viability of nuclear transfer embryos in sheep is not further compromised by knocking out the α1,3GT gene,* compared with controls.

In summary, this publication shows that the generation of α1,3G knockout sheep *poses no undue difficulty* beyond what is usually entailed in producing cloned knockout mammals by nuclear transfer. The method has been used successfully for recombination at the COL1A1 locus in sheep (McCreath et al., Nature 405:1066, 2000), and the α1,3GT locus in pigs (Phelps et al., *supra*).

Rejections under 35 USC § 112 ¶ 1:

Claims 1-6 and 33-37 stand rejected under § 112 ¶ 1 as not being adequately described or enabled by the specification. Applicant respectfully disagrees for the following reasons.

1. Some of the pending claims do not require that α1,3GT knockout sheep be produced

Claims 4, 5, and 33-37 cover ovine cell(s) which is heterozygous or homozygous for inactivation of an α1,3GT gene. It is not necessary to clone a sheep containing an inactivated α1,3GT gene for the embodiment recited in these claims to be described or enabled.

The patent specification provides working examples of cells having an inactivated α1,3GT gene in Examples 4 and 5 (page 50 ff), using targeting vectors illustrated in Example 3 (page 46 ff). The specification further describes methods for making homozygous knockout cells without first making a cloned sheep. See page 40, line 20 to page 41, line 13. The Denning article provides further illustrations of cells containing a α1,3GT knockout, and 60-day-old fetuses from which tissues of various kinds having a α1,3GT knockout could be harvested.

Issued U.S. Patent 5,821,117 discloses the porcine α1,3GT gene. Coverage includes the following claims:

1. An isolated nucleic acid molecule comprising:
   (a) the nucleic acid sequence of SEQ ID NO:1; or
   (b) an antisense sequence complementary to (a); or
   (c) both (a) and (b).

7. A porcine cell comprising an inactivated porcine α(1,3) galactosyl transferase gene, said inactivated porcine α(1,3) galactosyl transferase gene comprising a wild type porcine α(1,3) galactosyl transferase sequence disrupted by a cloned mutant porcine α(1,3) galactosyl transferase sequence, wherein the cloned mutant porcine α(1,3) galactosyl transferase sequence comprises a mutation of SEQ ID NO:1, wherein the mutation is selected from the group consisting of a deletion, an insertion, a substitution, and an addition such that the cloned mutant porcine α(1,3) galactosyl transferase sequence does not encode a functional galactosyl transferase so that immune reaction of the cell with human antibodies reactive with Gal α(1,3) Gal epitopes is avoided.

The enablement requirement is met if the description enables *any mode* of making and using the claimed invention. *Engel Industries, Inc. v. Lockformer Co.*, 20 USPQ2d 1300 (Fed. Cir. 1991). Accordingly, claims 4, 5, and 33-37 of the present application are described and enabled by the specification on this basis alone.

2. The Office has not established that α1,3GT knockout sheep cannot be made

The Patent Office has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention[1]. The basis provided by the Office to challenge the claimed invention under 112 ¶ 1 is:

(A) the specification does not provide an actual illustration of a homozygous α1,3GT knockout sheep;

(B) the "physiological art" in general is acknowledged to be unpredictable (citing MPEP § 2164.03);

(C) the Denning reference also dos not provide an actual illustration of a homozygous α1,3GT knockout sheep.

Applicants respectfully submit that this is inadequate to establish a *prima facie* case for unpatentability under 35 USC § 112 ¶ 1[2].

With regards to point (A), there is no requirement that an actual working example be provided in the specification in order for a patent disclosure to be enabling.

> It is well established in the law that a specification can adequately describe the manner and process of making an embodiment of an invention, whether or not it has actually been conducted. Use of prophetic examples does not make a patent non-enabling. The burden is on the person challenging the patent to show . . . that the prophetic examples together with other parts of the specification are not enabling. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 224 USPQ 409 (Fed. Cir. 1984).

With regards to point (B), there is no evidence of record that the art required for the practice of this invention is unpredictable. MPEP § 2164.04 has this to say about unpredictability:

> The "predictability or lack thereof" in the art refers to the ability of one skilled in the art o extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art.

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[1] *In re Wright*, 27 USPQ2d 1510 (Fed. Cir. 1993). It is incumbent upon the Office to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning. *In re Marzocchi* 169 USPQ 367, 370 (CCPA 1971). The examiner should specifically identify what information is missing and why one skilled in the art could not supply the information without undue experimentation. MPEP § 2164.04.

[2] [A]ny party making the assertion that a U.S. patent specification or claims fails, for one reason or another, to comply with § 112 bears the burden of persuasion in showing said lack of compliance. *Fiers v. Revel.*, 25 USPQ2d 1602 (Fed. Cir. 1993).

The method of cloning sheep by nuclear transfer is described, illustrated, and enabled in U.S. Patents 6,147,276; 6,252,133; and 6,525,243 (Campbell & Wilmut). In accordance with MPEP § 2164.04, the relevant question is whether knocking the α1,3GT gene would somehow affect the rate of nuclear transfer, which is already a known and enabled technology in the hands of the public. *The Office has provided no rationale or extrinsic evidence that supports the idea that change in cell surface glycosylation would in any way affect embryo viability.*

With regards to point (C), the Denning reference does not show that α1,3GT knockout sheep cannot be made. To the contrary. As explained above, the Denning reference shows that the viability of embryos after transfer into final recipients was at least as high with the α1,3GT knockout embryos as with the untransfected controls.

Since the Office has failed to dispel its initial burden of establishing a *prima facie* case for unpatentability under 35 USC § 112 ¶ 1, benefit of the doubt must be given to the applicant[3].

[3] [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971, affirmed in *Fiers v. Revel*, 25 USPQ2d 1602 (Fed. Cir. 1993); and *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995).

3. The post-filing evidence shows that α1,3GT knockout sheep are enabled by the application as filed

The publication by Phelps et al., provided in the accompanying IDS, and explained above, provides further confirmation that large animal α1,3GT homozygous knockouts can be made, providing that the practitioner has possession of α1,3GT knockout sequence for the same species. There are now several illustrations of species in which the Galα(1,3)Gal epitope and the α1,3GT gene are unnecessary for viability — either as embryos, or after birth:

- Humans, apes, and old world monkeys, which do not have the α1,3GT gene to begin with. Gailili et al., Proc. Natl. Acad. Sci. USA 15:7401, 1991.
- Homozygous α1,3GT knockouts have been made from mice. U.S. Patent 5,849,991 has issued claims to the mouse α1,3GT gene, α1,3GT knockout cells, and α1,3GT knockout mice.
- Phelps et al. (*supra*) illustrates that α1,3GT knockout pigs can be made by nuclear transfer techniques using the pig α1,3GT sequence (U.S. Patent 5,821,117).

All the evidence of record shows that the α1,3GT gene is not needed for survival, and that mammals get along perfectly well without it. There is no evidence that making α1,3GT knockouts for sheep should be more problematic than any other mammal. Whatever the frequency of successful nuclear transfer, it is not undue experimentation to repeat the procedure until a successful α1,3GT knockout is obtained in the sheep, just as Phelps et al. obtained it in the pig.

Thus, the claimed invention is both described and enabled by the specification, and the invention is patentable under 35 USC § 112 ¶ 1. Withdrawal of the rejections is respectfully requested.